Phase I/II study of weekly paclitaxel and carboplatin with concurrent radiation therapy in locally advanced non-small-cell lung cancer: Kansai Clinical Oncology Group T0401

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Abstract

Background: Concurrent chemoradiotherapy (CCRT) is effective in patients with unresectable stage III locally advanced non-small-cell lung cancer (NSCLC). Weekly carboplatin and paclitaxel is a common CCRT regimen, but with variable results. Phase I of this study evaluated the recommended paclitaxel dosage. Phase II assessed response rates, progression-free survival, overall survival and adverse events.

Materials and Methods: A high, monthly single dose of carboplatin instead of a weekly divided dose was administered, and the dose intensity was increased. In the phase I study, patients with stage III NSCLC were treated with two cycles of four weeks of 40–70 mg/m² intravenous paclitaxel on days 1, 8 and 15 with carboplatin (area under the concentration curve (AUC 5) on day 1, and concurrent radiation therapy of 60 Gy in 30 fractions (2 Gy per fraction, 5 fractions per week). The phase I study results determined the phase II paclitaxel dose. The phase II primary endpoint was the CCRT response rate and secondary endpoints were progression-free survival, overall survival and safety.

Results: Phase I enrolled 12 patients. Because of dose-limiting toxicities at 50 mg/m², the recommended paclitaxel dose was 40 mg/m². Phase II enrolled 19 patients with a median age of 66 (range 54–74) years, 17 were men, 11 had adenocarcinoma, 7 had squamous cell carcinoma and one had adenosquamous carcinoma. The response rate was 91.7%, progression-free survival was 11.7 months, and overall survival was 22.5 months. The incidence of grade 3 and 4 neutropaenia was 33% that of grade 2 or higher radiation pneumonitis was 15%.

Conclusion: Concurrent chemoradiation therapy with monthly carboplatin (AUC 5) and weekly paclitaxel (40 mg/m²) might be effective and feasible for locally advanced NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1], and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases [2]. Approximately 30% of patients with NSCLC present with locally advanced cancer [3]. Surgery is recommended for treatment stage III locally advanced NSCLC, but there are few resection candidates. In most unresectable cases, the standard treatment is combined thoracic radiotherapy (TRT) and chemotherapy [4–7]. Some randomised phase III studies of the timing of chemotherapy and radiotherapy reported that concurrent chemoradiation therapy (CCRT) significantly extended survival compared with sequential chemoradiation [8, 9].

National Comprehensive Cancer Network (NCCN) Guidelines recommend platinum-doublet chemotherapy during CCRT. Weekly paclitaxel and carboplatin is a frequently used regimen, but does not always have favourable outcomes compared with other regimens [10]. Because carboplatin reportedly has a dose–intensity relation [11], we, the Kansai Clinical Oncology Group (KCOG), hypothesised that a regimen with weekly low-dosage paclitaxel and monthly full dosage carboplatin would have enhanced anti-tumour effects. We conducted a phase I study to determine the recommended dosage of paclitaxel, and a phase II study to assess the efficacy and toxicity of this CCRT.

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**Material and methods**

### Eligibility

Patients with histologically or cytologically confirmed and unresectable stage III NSCLC were eligible for inclusion. Unresectable stage IIIA disease was defined by the presence of multiple or bulky N2 mediastinal lymph nodes on computed tomography (CT) or positron emission tomography (FDG-PET). Eligible patients also had no prior history of chemotherapy or TRT, were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, ≥ 20 and < 75 years of age, had leucocytes ≥ 4,000/mm³, neutrophils ≥ 2,000/mm³, platelets ≥ 100,000/mm³, haemoglobin ≥ 9.0 g/dL, serum creatinine ≤ 1.5 mg/dL, AST and ALT ≤ twice the upper limit of normal, partial pressure of arterial oxygen > 70 mmHg and no abnormalities on echocardiographic evaluation.

Patients with pulmonary fibrosis requiring oxygen therapy, myocardial infarction within the previous 6 months, liver cirrhosis, active haemorrhage of the digestive tract, a mental disorder requiring treatment, poorly controlled diabetes mellitus, paralytic ileus active infection, a history of radiation in the fields treated in this study, allergy to components of polyoxyethylene preparations, peripheral neuropathy, or pregnancy were excluded. Patients judged by a physician to be unable to participate were also excluded. The study protocol was approved by the ethics committee of the Tazuke Kofukai Medical Research Institute, Kitano Hospital and all other participating institutions. The study was conducted following the ethical guidelines of the Declaration of Helsinki. All patients gave written informed consent before enrolment. The period of registration and follow-up was from April 2005 to May 2011. This study was registered with the UMIN Clinical Trials Registry, receipt no. R000030549, ID. UMIN000026606.

### Study design

Treatment included initial concurrent chemoradiotherapy and subsequent consolidation chemotherapy. The phase I study was conducted to determine the recommended paclitaxel dosage. Chemotherapy began with paclitaxel at the designated dosage on days 1, 8, 15, 29 and 43, and carboplatin (AUC 5 mg/mL/min) on day 1. The initial paclitaxel dose was 40 mg/m². For consolidation chemotherapy, paclitaxel was fixed at 60 mg/m².

**Stage III NSCLC**

- **Concurrent chemoradiotherapy**
  - Paclitaxel (designated dose mg/m²/wk)
    - Days 1, 8, 15 q4 weeks × 2 cycles
    - Carboplatin (AUC = 5)
    - Day 1 q4 weeks × 2 cycles

- **Radiation**
  - 60 Gy
  - (2 Gy × 5 days/week × 6 weeks)

**Consolidation chemotherapy**

- Paclitaxel (60 mg/m²/wk)
  - Day 1, 8, 15 q4 weeks × 2 cycles
- Carboplatin (AUC = 5)
  - Day 1 q4 weeks × 2 cycles

*Figure 1. Design of study phase I.*
or dermatitis, pyrexia of 38°C or more, grade 2–4 pneumonitis, or an arterial oxygen partial pressure of less than 60 mmHg.

Efficacy and toxicity evaluation

All eligible patients were evaluated for treatment response and toxicity. Complete blood counts (CBCs) and blood chemistry studies were repeated weekly during treatment. Chest X-rays, thoracic computed tomography (CT) and tumour markers were evaluated monthly during treatment. After treatment, imaging studies including fluodeoxyglucose positron emission tomography (FDG–PET) and brain magnetic resonance imaging (MRI) were done if recurrence was suspected. Treatment response was evaluated by the Response Evaluation Criteria in Solid Tumours (RECIST) and response rates (RRs) were expressed as percentages of patients with complete response (CR) and partial response (PR). Disease control was reported as CR, PR and percentage of patients with stable disease (SD). Overall survival (OS) was the time from registration until death from any cause. Progression-free survival (PFS) was the time between registration and disease progression, death, or last known follow-up.

Statistical methods

The primary end point of the phase I study was the recommended dosage of paclitaxel during concurrent chemoradiotherapy. The primary endpoint of the phase II study was the treatment response rate; secondary endpoints were PFS, OS and safety. Evaluation of the feasibility of curative surgery was conducted following a cumulative 40 Gy radiation dose. Surgical cases were excluded from the evaluation of treatment effectiveness and toxicity. Patients who received the recommended phase I study dosage were included in the assessment of effectiveness. The response to concurrent chemoradiotherapy for unresectable locally advanced lung cancer has been estimated at 71%–78.6% [12–14]. When the lower limit of the expected response rate was 71%, 36 cases were required. Considering dropouts, the planned study registration was 40 patients in the phase II study. Cumulative OS and PFS were estimated by the Kaplan–Meier method. Statistical analysis was conducted with StatMate IV (ATMS Co. Ltd., Tokyo, Japan).

Results

Phase I study

A total of 12 patients, nine men and three women were included in the phase I study. The patient characteristics are shown in Table 1. The median age was 64 (43–74) years, three patients were stage IIIB, nine were stage IIIB, six patients were diagnosed with adenocarcinoma and the others with squamous cell carcinoma. DLT occurred at paclitaxel dose of 50 mg/m², which was designated as the MTD. DLT occurred in two patients. One had grade 4 neutropaenia, the other had to skip chemotherapy two or more times to receive the planned administration dosage. Therefore, the recommended concurrent chemotherapy paclitaxel dosage was 40 mg/m².

Phase II study

Recruitment was stopped at 5 years from the start of the study even though the planned enrolment had not been reached. A total of 19 patients were registered in the phase II study. The patient characteristics are shown in Table 1. Seventeen men and two women were included, the median age was 66 (54–74) years, 9 patients were stage IIIA; 10 were stage IIIB, 11 were diagnosed with adenocarcinoma, seven with squamous cell carcinoma and one with adenosquamous cell carcinoma. Three patients were excluded because they were ultimately treated with surgery. The RR of the phase II study was 93.8% [95% confidence interval (CI), 82–100%]. The disease control rate was 100%. If the eight patients administered the recommended dosage of paclitaxel in the phase I study were included in this analysis, then the response rate would be 91.8% (95% CI, 80.9–100%) and the disease control rate would be 100% (Table 2). The secondary endpoints, OS and median PFS, are shown in Fig. 2. Median survival time (MST) was 24.0 months; PFS was 14.8 months. When the eight patients in the phase I study were included, MST was 22.5 months and PFS 11.7 months. The three-year survival rate was 33.0%.

Grade 3 or more severe toxicities included neutropaenia, leucopenia, thrombocytopenia, radiation pneumonitis, infection and peripheral neuropathy (Table 3). A treatment-related death of a 70-year-old man who was hospitalised with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia on day 1 in the third course of chemotherapy was reported. The patient did not respond to antibiotics and eventually died. Nineteen of 27 patients (70%) completed the study. Delay of starting treatment or skipping treatment administration occurred in 12 patients.

Discussion

The study demonstrated a good treatment response to and satisfactory tolerability of quad-weekly carboplatin (AUC 5) and weekly paclitaxel (40 mg/m²) combined with concurrent TRT of 60 Gy followed by quad-weekly carboplatin (AUC 5) and weekly paclitaxel (60 mg/m²) in patients with NSCLC. In the phase I study, the appropriate dosage of paclitaxel was 40 mg/m². In the phase II study, RR was 93.8%; PFS was 11.7 months, and OS was 24 months. The most common grade 3 or more severe adverse event was neutropaenia, which was observed in 33.0% of patients.

Paclitaxel and carboplatin-including CCRT regimens for NSCLC used in previous studies are shown in Table 4. Decreasing doses of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase I (N = 12)</th>
<th>Phase II (N = 19)</th>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
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<td>3 25</td>
<td>2 11</td>
</tr>
<tr>
<td>Male</td>
<td>9 75</td>
<td>17 89</td>
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<td>11 58</td>
</tr>
<tr>
<td>Squamous cell ca.</td>
<td>6 50</td>
<td>7 37</td>
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<tr>
<td>Other</td>
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Table 2. Response rate (RR) and disease control rate (DCR)
Table 4. Previous studies that used paclitaxel CCRT regimens

<table>
<thead>
<tr>
<th>Treatment schedule</th>
<th>RR (%)</th>
<th>MST (months)</th>
<th>3-yr survival (%)</th>
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<td>RTOG 9801 Phase III</td>
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<tr>
<td>1. PC→PwCw+HfxRT+AMO</td>
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<td>1.7 17.3</td>
<td>1. 28 28</td>
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<tr>
<td>2. PC→PwCw+HfxRT</td>
<td></td>
<td>1.7 17.9</td>
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<tr>
<td>WJTOG0105 Phase III</td>
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<tr>
<td>1. MVP→XRT</td>
<td>6.6 2.6.6</td>
<td>20.5 20.5</td>
<td>2. 35 35</td>
</tr>
<tr>
<td>2. CPT-11+CBPw+XRT</td>
<td>63.0 63.0</td>
<td>19.8 19.8</td>
<td>2. 24 24</td>
</tr>
<tr>
<td>3. PwCw+XRT</td>
<td>63.7 63.7</td>
<td>22.0 22.0</td>
<td>2. 26 26</td>
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<tr>
<td>Luhua et al. Randomized Phases II</td>
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<td>20.2 20.2</td>
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<tr>
<td>PwCw+XRT</td>
<td>91.7</td>
<td>22.5</td>
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In conclusion, CCRT with monthly carboplatin (AUC 5) and weekly paclitaxel (40 mg/m²) was an effective and tolerable regimen for these NSCLC patients. Increased dose-intensity may explain the effectiveness benefit of not dividing the carboplatin dose, but there were too few subjects to make a confident conclusion. A phase III study to compare this protocol with weekly carboplatin and weekly paclitaxel and TRT is warranted.

**Competing interests**

All authors have no competing interests.
Authors’ contributions

Kazufumi Takamatsu performed the statistical analysis and wrote the manuscript. Takehisa Takagi performed the radiotherapy and supervised the research of radiation part. Kiyoshi Komuta, Tadashi Mio and Masataka Hirabayashi collected the patients data. Satoshi Marumo and Motonori Fukui supervised the research and revised the manuscript. All authors have read and approved the final version of the manuscript.

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References